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(54) **Tablet for pharmaceutical use with release at successive times.**

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EP 0 274 734 B1

Description

This invention relates to a tablet for pharmaceutical use able to release active substances at successive times.

More specifically, the invention relates to a multi-layer tablet able to release different portions of the same or of different substances at successive times into the aqueous fluid with which it comes into contact.

The invention is particularly suitable for use in the medicinal field but can be generally used in all sectors in which active substances have to be released at different times spaced apart by a predetermined time interval, such as in the fertilizer, herbicide and other sectors.

It is well known that the success of a therapy depends not only on the correct choice of medicament but also on whether its formulation is optimum from the technical and biopharmaceutical viewpoint.

In some cases the active substance must be released from the pharmaceutical form at constant rate to enable a constant hematic concentration within a therapeutically effective range to be maintained for the entire duration of treatment. This result can be obtained by using pharmaceutical forms of controlled release type from which the active principle is released at a constant rate for the time necessary to obtain the desired effect.

In other cases a constant hematic concentration of the medicament is not suitable; in this respect, certain morbid symptoms such as rheumatic and cardiac illnesses require high hematic concentrations to be reached for a limited time period.

This result can be easily obtained by frequently administering pharmaceutic forms which give instant release of the active substances, to thus define a complex posology scheme which is however not easily implemented by the patient.

French patent 2.100.858 discloses the manufacturing of tablets having multilayer structure which affords a drug release control owing to the different dissolution rate of the single layers, nevertheless the proposed compositions not always give optimal results.

With the present invention we have conceived a new pharmaceutical form which enables the active substances contained in it to be released in successive spaced-apart stages, to therefor obtain high hematic medicament levels at successive time intervals.

In this manner the posology scheme is simplified and the acute pain symptomatology manifested in these illnesses at determined intervals (such as morning pain in rheumatic illness) can be more appropriately resolved.

Basically, the tablet of the present invention enables the number of administrations of active substance to be reduced, with undoubted practical advantages.

The tablet for releasing active substances at successive times according to the invention is characterised by comprising at least: a first layer containing a portion of the active substance and suitable excipients, a barrier layer of polymer material,gellable and/or soluble on contact with water and/or aqueous liquids, which is interposed between said first layer and a third layer containing the remaining portion of active substance with suitable excicpients, said barrier layer and said third layer being housed in a casing consisting of polymer material impermeable to and insoluble in water or soluble in an alkaline environment.

These and other characteristics and advantages of the tablet according to the invention will be mare apparent from the detailed description of preferred embodiments given hereinafter by way of non-limiting example.

A schematic representation of one embodiment of the tablet according to the present invention is shown in Figure 1 in which the reference numerals 1, 2, and 3 indicate the first, second and third tablet layer respectively, and 4 indicates the casing, the second layer being obviously the barrier layer.

In said embodiment, the tablet of the present invention therefore consists of two separate deposits of active substance 1 and 3, separated from each other by a layer 2 of gellable and/or soluble polymer material.

The tablet can also consist of more than two of said deposits of active substance separated from each other by layers of said polymer material, and in addition the active substance can be of the same or different type in the various deposits.

The active substance release mechanism is the following: on contact with water or aqueous liquid, the uncovered part 1 of the tablet rapidly disintegrates; this therefore results in release of the first medicament portion, leaving as residue the casing 4 closed by the barrier layer 2 and containing the second medicament portion in 3.

At this point the barrier layer comes into contact with the water and interacts with it; this interaction is gradual, in the sense that the water penetrates at a rate controlled by the components of the barrier layer itself.

The time required for the barrier layer to be traversed by the water is controlled not only by the composition but also by the thickness of the barrier. The result of this contact between the water and barrier is that the barrier is converted from a solid into a viscous gel with consequent weakening of its rupture resistance properties. When a sufficient quantity of water has passed through the barrier and made contact with the layer 3, the materials contained in this layer swell, so destroying the barrier layer 2 and allowing the contents to escape.

The medicament release mechanism is therefore based in practice on successive interaction of the various material layers with water in the following sequence:

- rapid interaction of the unprotected part 1 with release of the first medicament portion,
- slow interaction of the barrier layer 2 and its gelling,
- rapid interaction of the remainder 3 with development of a force able to demolish the gelled barrier and release the second medicament portion.

The described mechanism also applies to the other layers of a tablet having a larger number of layers.

The rate of gelling and/or of solubilization of the barrier layer and/or of the casing is the factor which controls the release of the second portion of active substance.

The rate of release of the active substance from the layers containing it can be varied according to therapeutic needs, and this can be done by varying the composition of the layer concerned.

Each layer of active substance contains, in mixture with the active substance, materials which on contact with water and/or aqueous liquids are able to develop a disintegration force by swelling or by gas formation.

This disintegration force constitutes the source of energy able to determine the release of the active substance from the deposit containing it.

Materials able to supply this disintegration force are those of the so-called "superdisintegrator" class and are usually polymers of natural or synthetic origin for human and veterinary pharmaceutical use.

These materials comprise for example: carboxymethylamide, cross-linked sodiumcarboxymethylcellulose, cross-linked polyvinylpyrrolidone, and cross-linked hydroxypropylmethylcellulose.

Depending on the characteristics of the active substance, inorganic substances can also be used as disintegrators, such as bases and/or acids which when in contact with water are able to react chemically with the active substance or with other excipients of the formulation to give rise to gaseous substances which lead to the rapid disintegration of the layer and thus to the release of the active principle.

Sodium bicarbonate, sodium carbonate, magnesium peroxide etc. are the preferred acids and bases.

In addition to the active substance and disintegration substances, other materials can be used in the formulation which are able to give the mixture the characteristics necessary for its transformation into its finished form.

A basic characteristic of the constituent mixtures of the individual layers is that they are able to be easily compressed or compacted in accordance with the known art.

In each layer containing the active substance, the quantity of swellable material and/or material able to cause disintegration of the layer when it comes into contact with water is between 1% and 95% of the total weight of the layer. The layer composition can also comprise other so-called excipients such as diluents, lubricants, dyes etc., such as magnesium stearate, talc, colouring and the like in a quantity variable from 0.5% to 90%. The active substance present in an individual layer is between 0.1 and 95% of the weight of the layer.

The active substance itself can be prepared in microencapsulated form, ie in solid particles covered with polymer material able to transfer the active substance gradually and/or in accordance with the pH variations of the gastro-intestinal tract.

For the barrier layer, polymers are used chosen from cellulose derivatives such as hydroxypropylmethylcellulose, methylcellulose or polyvinylalcohols of various molecular weights, and other excipients can be added such as mannitol, talc, polyvinylpyrrolidone and magnesium stearate.

The casing generally consists of filmogen polymer substances insoluble in and impermeable to water, and can be natural, synthetic or semisynthetic substances such as ethylcellulose, cellulose-acetate-propionate, methacrylic polymers, acrylic and methacrylic copolymers and polyalcohols. Water-insoluble polymers are preferably used, but in certain embodiments polymers soluble in an alkaline environment can be used to facilitate destruction of the casing when in the enteric tract. Biodegradable polymers can also be used.

The tablets are formed by a multilayer tablet press able to exert in the final compression stage a pressure of about 3000 kg/cm^2.

The mixture for forming the casing can be applied by various methods such as spraying, compression or immersion, or the tablet parts can be inserted into a preformed casing.

EXAMPLE 1

Preparation of tablets containing ibuprofen as active substance.

a) Preparation of ibuprofen granulate.

To prepare 1000 tablets the following materials were used in the quantities stated:

Ibuprofen	600 g
Corn starch	120 g
Methylcellulose	4.5 g

The ibuprofen and corn starch were poured into a powder mixer and the mixture wetted with a 2.5% solution of methylcellulose in 1:1 ethanol: water using about 180 ml of solution. The mixture when wetted homogeneously was forced through an 800 µm screen to obtain a granulate which after partial drying was passed through a 420 µm screen in accordance with the known art. The granulate was further dried in a tray drier until of constant weight, after which the following were added:

- sodium bicarbonate	15 g
- sodium carboxymethylamide (Primojel)	15 g
- cross-linked polyvinylpyrrolidone (Polyplasdone)	15 g
- magnesium stearate	4 g

The component mixture was mixed until a homogeneous product was obtained.

b) Preparation of barrier layer material.

The following were used to prepare 1000 barrier layers for tablet preparation:

Hydroxypropylmethylcellulose (low molecular weight - Methocel)	7.5 g
Hydroxypropylmethylcellulose (medium molecular weight - Methocel)	2.5 g
Mannitol	20 g
Talc	14 g
Polyvinylpyrrolidone	6 g
Yellow colouring	1 g
Mg stearate	0.5 g

The hydroxypropylmethylcellulose, mannitol, talc and yellow colouring were mixed in a powder mixer; the mixture was wetted with a solution of polyvinylpyrrolidone in alcohol and the wet mass was forced through a 420 µm screen.

The granulate was dried in an oven and was then mixed with magnesium stearate.

c) Preparation of tablets.

The tablets were prepared without their casing using a multilayer tablet press with three loading

stations; the first and third station were fed with the granulate containing ibuprofen prepared as described under point a), the second loading station being fed with the polymer granulate prepared for the barrier layer as indicated under point b).

The machine, fitted with circular dished punches of 13 mm diameter, was adjusted to feed a granulate quantity equivalent to 300 mg of active substance from stations 1 and 3 and granulate quantity of about 100 mg from station 2. The machine pressure was adjusted to allow a pressure of about 3000 kg/cm^2 to be exerted in the final compression stage.

Operating as described, at the end of the working cycle convex-based cylindrical tablets were obtained weighing about 900 mg and having two layers of active substance and a regular, homogeneous barrier layer of gellable polymer material, separating the two layers of active substance.

d) Application of the casing.

The tablets obtained as described were positioned in a suitable container provided with regularly positioned circular cavities able to only partly contain a prepared tablet when positioned horizontally, to leave an exposed portion comprising a layer of active substance and the barrier layer.

Using a suitable spray system, the exposed surface of the tablets was sprayed with a solution consisting of:

Ethylcellulose (Ethocel)	**16 g**
Diethyl phthalate	**4 g**
Ethanol	**10 g**
Ethyl acetate	**12 g**
Toluene	**45 g**
Butyl acetate	**13 g**

e) "In vitro" evaluation of tablet characteristics.

1) disintegration test.

The apparatus of U.S.P. XXI was used to evaluate the tablet disintegration rate.

6 tablets were placed in the baskets and the prescribed procedure was followed using water at 37° C as the disintegration fluid.

The first tablet layer containing the first medicament portion (300 mg) disintegrated in 5 minutes, after which time the second medicament portion contained in the third layer was completely unaltered, this portion being protected on its top by the gellable polymer barrier and on its sides and bottom by the impermeable and insoluble polymer membrane.

As the disintegration test proceeded a slow hydration of the barrier layer was noted, with an increase in volume of the barrier, gelling and weakening of the layer and slow erosion and/or solubilization.

During this stage the barrier layer became progressively permeable to the disintegration liquid, to enable water, after a time of about 0.5-1 hours, to come into contact with the second layer of the system containing the second portion of active principle.

When the water or aqueous fluid comes into contact with the third layer it swells to destroy the gelled barrier, with emergence of the ibuprofen particles in a time of about 15 minutes.

During the entire disintegration process the insoluble and impermeable polymer coating around the tablet preserves its characteristics and therefore at the end of the disintegration process it remains as a completely empty cylindrical container.

2) Dissolution tests.

The "in vitro" tests to determine the release of active substance from the tablets were conducted using as the dissolution apparatus the six-position basket scheduled for the U.S.P. XXI disintegration test.

1000 ml of simulated intestinal fluid at pH 7.2 and at a temperature of 37° C were used as the

dissolution fluid.

Using the tablets prepared as in Example 1, the following results were obtained:

time (minutes)	% fraction released (of the 1st portion of 300 mg of active substance contained in the 1st layer)
2	50%
4	75%
6	85%
8	92%
10	100%
35	Membrane hydration
	% fraction released (of the 2nd portion of 300 mg of active substance contained in the 3rd layer)
40	30%
50	100%

3) "In vivo" evaluation of the tablets

The tablets prepared as in Example 1 were administered to healthy volunteers and gave the following plasmatic levels of active substance:

time (hours)	plasmatic concentration (mcg/ml)
1	25.8
2	22.3
4	14.3
6	5.7
8	8.1
10	9.6
12	10.5
24	4.0

EXAMPLE 2

Preparation of tablets containing propanolol HCl as active substance

a) Preparation of propanolol HCl granulate.

To prepare 10000 tablets the following materials were used in the quantities stated:

Propanolol HCC	400	g
Corn starch	1000	g
Methylcellulose	10	g
Sodium laurylsulphate	5	g

The propanolol HCl and corn starch sieved to 420 µm were poured into a powder mixer and the mixture wetted with a 1.3% solution of methylcellulose in water containing the stated quantity of sodium laurylsulphate. The mixture when wetted homogeneously was forced through an 800 µm screen to obtain a granulate which after partial drying was passed through a 420 µm screen in accordance with the known art. The granulate was further dried in a tray drier until of constant weight, after which the following were added:

- sodium carboxymethylamide (Primojel)	110	g
- corn starch	260	g
- cross-linked polyvinylpyrrolidone (Polyplasdone)	46	g
- microcrystalline cellulose (Avicel pH 101)	185	g
- magnesium stearate	15	g

The component mixture was mixed until a homogeneous product was obtained.

b) Preparation of barrier layer material.

The following were used to prepare 10000 barrier layers for tablet preparation:

Hydroxypropylmethylcellulose (low molecular weight - Methocel KM4)	97.5	g
Hydroxypropylmethylcellulose (medium molecular weight - Methocel K15M)	32.5	g
Mannitol	260.0	g
Talc	182.0	g
Polyvinylpyrrolidone	78.0	g
Yellow colouring	13.0	g
Mg stearate	6.5	g

The hydroxypropylmethylcellulose, mannitol, talc and yellow colouring were mixed in a powder mixer; the mixture was wetted with a solution of polyvinylpyrrolidone in alcohol and the wet mass was forced through a 420 µm screen. The granulate was dried in an oven and was then mixed with magnesium stearate.

c) Preparation of propanolol HCl tablets.

The tablets were prepared without their casing using a multilayer tablet press with three loading stations, the first and third station were fed with the granulate containing propanolol HCl prepared as described under point a), the second loading station being fed with the polymer granulate prepared for the barrier layer as indicated under point b). The machine, fitted with circular flat punches of 10 mm diameter,

was adjusted to feed a granulate quantity of 200 mg equivalent to 40 mg of active substance from stations 1 and 3 and a quantity of about 65 mg from station 2.

The machine pressure was adjusted to allow a pressure of about 3000 kg/cm^2 to be exerted in the final compression stage. Operating as described, at the end of the working cycle flat-based cylindrical tablets were obtained weighing about 465 mg and having two layers of active substance and a regular, homogeneous barrier layer of gellable polymer material, separating the two layers of active substance.

d) Application of the casing

The tablets obtained as described were placed in a suitable container provided with regularly positioned circular cavities able to only partly contain a prepared tablet when positioned horizontally, to leave an exposed portion comprising a layer of active substance and the barrier. Using a suitable spray system, the exposed surface of the tablets was sprayed with a solution

consisting of:

- copolymer of acrylic and methacrylic acids (Eudragit S 100)	5.0 g
- castor oil	0.5 g
- acetone	37.8 g
- isopropanol	56.7 g

e) "In vitro" evaluation of tablet characteristics.

1) disintegration test.

The apparatus of U.S.P. XXI was used to evaluate the tablet disintegration rate. 6 tablets were placed in the baskets and the prescribed procedure was followed using gastric fluid (pH 1.2) at 37° C as the disintegration fluid.

The first tablet layer containing the first medicament portion (40 mg) disintegrated in 9 minutes, after which time the second medicament portion contained in the third layer was completely unaltered, this portion being protected on its top by the gellable polymer barrier and on its sides and bottom by the impermeable and insoluble polymer membrane.

As the disintegration test proceeded a slow hydration of the barrier layer was noted, with an increase in volume of the barrier, gelling and weakening of the layer and slow erosion and/or solubilization.

During this stage the barrier layer became progressively permeable to the disintegration liquid, to enable water, after a time of about 0.5-1 hours, to come into contact with the second layer of the system containing the second portion of active principle. When the water or aqueous fluid comes into contact with the third layer it swells to destroy the gelled barrier, with emergence of the propanolol HCl particles contained in the second layer. During the entire disintegration process the insoluble and impermeable polymer coating around the tablet preserves its characteristics and therefore at the end of the disintegration process it remains as a completely empty cylindrical container.

2) Dissolution tests.

The "in vitro" tests to determine the release of active substance from the tablets were conducted using as the dissolution apparatus the six-position basket prescribed for the U.S.P. XXI disintegration test. 1000 ml of simulated gastric fluid at pH 1.2 and at a temperature of 37° C were used as the dissolution fluid. Using the tablets prepared as in Example 2, the following results were obtained:

time (minutes)	% released (*)
2	18.4%
4	33.5%
6	44.0%
8	52.5%
10	58.8%
15	73.0
20	85.0
35	Membrane hydration
	% released (°)
5	4.6%
25	10.6%
45	18.3%
65	63.0%
75	74.8%
85	81.4%

(*) Of the first portion of 40 mg of active substance contained in the first layer.

(°) Of the second portion of 40 mg of active substance contained in the third layer.

EXAMPLE 3

Preparation of tablets containing acid indomethacin as active substance

a) Preparation of acid indomethacin granulate.

To prepare 10000 tablets the following materials were used in the quantities stated:

Acid indomethacin	350	g
Corn starch	1000	g
Methylcellulose	10	g
Sodium laurylsulphate	5	g

The indomethacin and corn starch sieved to 420 µm were poured into a powder mixer and the mixture wetted with a 1.3% solution of methylcellulose in water containing the stated quantity of sodium laurylsulphate. The mixture when wetted homogeneously was forced through an 800 µm screen to obtain a granulate which after partial drying was passed through a 420 µm screen in accordance with the known art.

The granulate was further dried in a tray drier until of constant weight, after which the following were added:

- sodium carboxymethylamide (Primojel)	110 g
- corn starch	260 g
- cross-linked polyvinylpyrrolidone (Polyplasdone)	46 g
- magnesium stearate	15 g

The component mixture was mixed until a homogeneous product was obtained.

b) Preparation of barrier layer material.

The following were used to prepare 10000 barrier layers for tablet preparation:

- hydroxypropylmethylcellulose (low molecular weight - Methocel KM4)	97.5 g
- hydroxypropylmethylcellulose (medium molecular weight - Methocel K15M)	32.5 g
- mannitol	260.0 g
- talc	182.0 g
- polyvinylpyrrolidone	78.0 g
- yellow colouring	13.0 g
- Mg stearate	6.5 g

The hydroxypropylmethylcellulose, mannitol, talc and yellow colouring were mixed in a powder mixer; the mixture was wetted with a solution of polyvinylpyrrolidone in alcohol and the wet mass was forced through a 420 µm screen. The granulate was dried in an oven and was then mixed with magnesium stearate.

c) Preparation of acid indomethacin tablets.

The tablets were prepared without their casing using a multilayer tablet press with three loading stations; the first and third station were fed with the indomethacin granulate prepared as described under point a), the second loading station being fed with the polymer granulate prepared for the barrier layer as indicated under point b). The machine, fitted with circular flat punches of 10 mm diameter, was adjusted to feed a granulate quantity of 180 mg equivalent to 35 mg of active substance from stations 1 and 3 and a quantity of about 65 mg from station 2.

The machine pressure was adjusted to allow a pressure of about 3000 kg/cm^2 to be exerted in the final compression stage. Operating as described, at the end of the working cycle flat-based cylindrical tablets were obtained weighing about 425 mg and having two layers of active substance and a regular, homogeneous barrier separating the two layers of active substance.

d) Application of the casing.

The tablets obtained as described were placed in a suitable container provided with regularly positioned circular cavities able to only partly contain a prepared tablet when positioned horizontally, to leave an exposed portion comprising a layer of active substance and the barrier.

Using a suitable spray system, the exposed surface of the tablets was sprayed with a solution

consisting of:

- copolymer of acrylic and methacrylic acids (Eudragit S 100)	5.0 g
- castor oil	0.5 g
- acetone	37.8 g
- isopropanol	56.7 g

e) "In vitro" evaluation of tablet characteristics.

1) disintegration test.

The apparatus of U.S.P. XXI was used to evaluate the tablet disintegration rate. 6 tablets were placed in the baskets and the prescribed procedure was followed using gastric fluid (pH 1.2) at 37° C as the disintegration fluid.

The first tablet layer-containing the first medicament portion (35 mg) disintegrated in 5 minutes, after which time the second medicament portion contained in the third layer was completely unaltered, this portion being protected on its top by the gellable polymer barrier and on its sides and bottom by the impermeable and insoluble polymer membrane.

As the disintegration test proceeded a slow hydration of the barrier layer was noted, with an increase in volume of the barrier, gelling and weakening of the layer and slow erosion and/or solubilization.

During this stage the barrier layer became progressively permeable to the disintegration liquid, to enable water, after a time of about 0.5-1 hours, to come into contact with the second layer of the system containing the second portion of active principle.

When the water or aqueous fluid comes into contact with the third layer it swells to destroy the gelled barrier, with emergence of the indomethacin particles contained in the second layer. During the entire disintegration process the insoluble and impermeable polymer coating around the tablet preserves its characteristics and therefore at the end of the disintegration process it remains as a completely empty cylindrical container.

2) Dissolution tests.

The "in vitro" tests to determine the release of active substance from the tablets were conducted using as the dissolution apparatus the six-position basket prescribed for the U.S.P. XXI disintegration test. 1000 ml of simulated intestinal fluid at pH 7.2 and at a temperature of 37° C were used as the dissolution fluid. Using the tablets prepared as in Example 3, the following results were obtained:

time (seconds)	percentage released (*)
60	29.9%
90	46.0%
120	57.0%
150	64.4%
180	71.0%
210	78.0%

(minutes)	Membrane hydration
35	percentage released (°)
15	30.5%
25	45.4%
35	56.8%
45	64.4%
55	70.6%
65	73.0%
75	78.4%

(*) Of the first portion of 35 mg of active substance contained in the first layer.

(°) Of the second portion of 35 mg of active substance contained in the third layer.

EXAMPLE 4

Preparation of tablets containing sodium naproxen as active substance

a) Preparation of sodium naproxen granulate.

To prepare 1000 tablets the following materials were used in the quantities stated:

sodium naproxen	275	g
corn starch	40	g
methylcellulose	1.5	g
sodium laurylsulphate	1	g

The sodium naproxen and corn starch sieved to 420 µm were poured into a powder mixer and the mixture wetted with a 1.3% solution of methylcellulose in water containing the stated quantity of sodium laurylsulphate. The mixture when wetted homogeneously was forced through an 800 µm screen to obtain a granulate which after partial drying was passed through a 420 µm screen in accordance with the known art. The granulate was further dried in a tray drier until of constant weight, after which the following were added:

- sodium carboxymethylamide (Primojel)	15 g
- corn starch	33 g
- cross-linked polyvinylpyrrolidone (Polyplasdone)	31 g
- magnesium stearate	4 g

The component mixture was mixed until a homogeneous product was obtained.

b) Preparation of barrier layer material.

The following were used to prepare barrier layers for tablet preparation:

- hydroxypropylmethylcellulose (low molecular weight - Methocel KM4)	15.0 g
- hydroxypropylmethylcellulose (medium molecular weight - Methocel K15M)	5.0 g
- mannitol	40.0 g
- talc	28.0 g
- polyvinylpyrrolidone	12.0 g
- yellow colouring	2.0 g
- Mg stearate	1.0 g

The hydroxypropylmethylcellulose, mannitol, talc and yellow colouring were mixed in a powder mixer; the mixture was wetted with a solution of polyvinylpyrrolidone in alcohol and the wet mass was forced through a 420 µm screen. The granulate was dried in an oven and was then mixed with magnesium stearate.

c) Preparation of sodium naproxen tablets.

The tablets were prepared without their casing using a multilayer tablet press with three loading stations; the first and third station were fed with the granulate containing sodium naproxen prepared as described under point a), the second loading station being fed with the polymer granulate prepared for the barrier layer as indicated under point b). The machine, fitted with circular flat punches of 13 mm diameter, was adjusted to feed a granulate quantity of 400 mg equivalent to 275 mg of active substance from stations 1 and 3 and a quantity of about 100 mg from station 2.

The machine pressure was adjusted to allow a pressure of about 3000 kg/cm^2 to be exerted in the final compression stage. Operating as described, at the end of the working cycle flat-based cylindrical tablets were obtained weighing about 900 mg and having two layers of active substance and a regular, homogeneous barrier separating the two layers of active substance.

d) Application of the casing.

The tablets obtained as described were placed in a suitable container provided with regularly positioned circular cavities able to only partly contain a prepared tablet when positioned horizontally, to leave an exposed portion comprising a layer of active substance and the barrier.

Using a suitable spray system, the exposed surface of the tablets was sprayed with a solution consisting of:

- copolymer of acrylic and methacrylic acids (Eudragit S 100)	5.0 g
- castor oil	0.5 g
- acetone	37.8 g
- isopropanol	56.7 g

e) "In vitro" evaluation of tablet characteristics.

1) disintegration test.

The apparatus of U.S.P. XXI was used to evaluate the tablet disintegration rate. 6 tablets were placed in the baskets and the prescribed procedure was following using gastric fluid (pH 1.2) at 37° C as the disintegration fluid. The first tablet layer containing the first medicament portion (274 mg) disintegrated in 5 minutes, after which time .the second medicament portion contained in the third layer was completely unaltered, this portion being protected on its top by the gellable polymer barrier and on its sides and bottom by the impermeable and insoluble polymer membrane.

As the disintegration test proceeded a slow hydration of the barrier layer was noted, with an increase in volume of the barrier, gelling and weakening of the layer and slow erosion and/or solubilization. During this stage the barrier layer became progressively permeable to the disintegration liquid, to enable water, after a time of about 0.5-1 hours, to come into contact with the second layer of the system containing the second portion of active principle.

When the water or aqueous fluid comes into contact with the third layer it swells to destroy the gelled barrier, with emergence of the sodium naproxen particles contained in the second layer. During the entire disintegration process the insoluble and impermeable polymer coating around the tablet preserves its characteristics and therefore at the end of the disintegration process it remains as a completely empty cylindrical container.

2) Dissolution tests.

The "in vitro" tests to determine the release of active substance from the tablets were conducted using as dissolution apparatus the six-position basket prescribed for the U.S.P. XXI disintegration test. 1000 ml of simulated intestinal fluid at pH 7.2 and at a temperature of 37° C were used as the dissolution fluid. Using the tablets prepared as in Example 4, the following results were obtained:

time (minutes)	Percentage released (*)
2	23%
4	41%
6	53%
8	68%
10	78%
35	Membrane hydration
	Percentage released (°)
5	49%
10	70%
15	88%

(*) Of the first portion of 275 mg of active substance contained in the first layer.

(°) Of the second portion of 275 mg of active substance contained in the third layer.

EXAMPLE 5

Preparation of tablets containing ibuprofen as active substance

a) Preparation of ibuprofen granulate.

To prepare 4000 tablets the following materials were used in the quantities stated:

ibuprofen	600	g
corn starch	80	g
methylcellulose	3	g
sodium laurylsulphate	2	g

The ibuprofen and corn starch sieved to 420 μm were poured into a powder mixer and the mixture wetted with a 1.3% solution of methylcellulose in water containing the stated quantity of sodium laurylsulphate. The mixture when wetted homogeneously was forced through an 800 μm screen to obtain a granulate which after partial drying was passed through a 420μm screen in accordance with the known art. The granulate was further dried in a tray drier until of constant weight, after which the following were added:

- sodium carboxymethylamide (Primojel)	30	g
- corn starch	66	g
- cross-linked polyvinylpyrrolidone (Polyplasdone)	12	g
- magnesium stearate	8	g

The component mixture was mixed until a homogeneous product was obtained.

b Preparation of barrier layer material.

The following were used to prepare barrier layers for tablet preparation:

- hydroxypropylmethylcellulose (low molecular weight - Methocel KM4)	60.0 g
- hydroxypropylmethylcellulose (medium molecular weight - Methocel K15M)	20.0 g
- mannitol	160.0 g
- talc	112.0 g
- polyvinylpyrrolidone	48.0 g
- yellow colouring	8.0 g
- Mg stearate	4.0 g

The hydroxypropylmethylcellulose, mannitol, talc and yellow colouring were mixed in a powder mixer; the mixture was wetted with a solution of polyvinylpyrrolidone in alcohol and the wet mass was forced through a 420 µm screen. The granulate was dried in an oven and was then mixed with magnesium stearate.

c) Preparation of ibuprofen tablets.

The tablets were prepared without their casing using a multilayer tablet press with three loading stations; the first and third station were fed with the ibuprofen granulate prepared as described under point a), the second loading station being fed with the polymer granulate prepared for the barrier layer as indicated under point b). The machine, fitted with circular flat punches of 10 mm diameter, was adjusted to feed a granulate quantity of 200 mg equivalent to 150 mg of active substance from stations 1 and 3 and a quantity of about 65 mg from station 2.

The machine pressure was adjusted to allow a pressure of about 3000 kg/cm^2 to be exerted in the final compression stage. Operating as described, at the end of the working cycle flat-based cylindrical tablets were obtained weighing about 465 mg and having two layers of active substance and a regular, homogeneous barrier layer separating the two layers of active substance.

d) Application of the casing.

The tablets obtained as described were placed in a suitable container provided with regularly positioned circular cavities able to only partly contain a prepared tablet when positioned horizontally, to leave an exposed portion comprising a layer of active substance and the barrier.

Using a suitable spray system, the exposed surface of the tablets was sprayed with a solution consisting of:

- copolymer of acrylic and methacrylic acids (Eudragit S 100)	5.0 g
- castor oil	0.5 g
- acetone	37.8 g
- isopropanol	56.7 g

e) "In vitro" evaluation of tablet characteristics.

1) disintegration test.

The apparatus of U.S.P. XXI was used to evaluate the tablet disintegration rate. 6 tablets were placed in the baskets and the prescribed procedure was followed using gastric fluid (pH 1.2) at 37° C as the disintegration fluid. The first tablet layer containing the first medicament portion (175 mg) disintegrated in 5 minutes, after which time the second medicament portion contained in the third layer was completely unaltered, this portion being protected on its top by the gellable polymer barrier and on its sides and bottom by the impermeable and insoluble polymer membrane.

As the disintegration test proceeded a slow hydration of the barrier layer was noted, with an increase in volume of the barrier, gelling and weakening of the layer and slow erosion and/or solubilization. During this stage the barrier layer became progressively permeable to the disintegration liquid, to enable water, after a time of about 0.5-1 hours, to come into contact with the second layer of the system containing the second portion of active principle.

When the water or aqueous fluid comes into contact with the third layer it swells to destroy the gelled barrier, the emergence of the ibuprofen particles contained in the second layer. During the entire disintegration process the insoluble and impermeable polymer coating around the tablet preserves its characteristics and therefore at the end of the disintegration process it remains as a completely empty cylindrical container.

2) Dissolution tests.

The "in vitro" tests to determine the release of active substance from the tablets were conducted using as dissolution apparatus the six-position basket prescribed for the U.S.P. XXI disintegration test. 1000 ml of simulated intestinal fluid at pH 7.2 and at a temperature of 37° C were used as the dissolution fluid. Using the tablets prepared as in Example 5, the following results were obtained:

time (seconds)	Percentage released (%)
15	1.5%
45	5 %
75	13.3%
105	28.6%
135	45.3%
165	60.5%
195	69 %
225	75.6%
255	80.6
(minute)	
35	Membrane hydration

	Percentage released (*)
8	7.3%
18	9.0%
28	10.3%
38	23.0
48	55.8
68	63.1%
78	70.2%
88	78.8%

(#) Of the first portion of 150 mg of active substance contained in the first layer.

(*) Of the second portion of 150 mg of active substance contained in the third layer.

Claims

1. A tablet for pharmaceutical use able to release an active substance at successive times, comprising:
   a) a first layer containing a first portion of an active substance, at least one disintegrant substance which on contact with water or aqueous liquids is able to develop a disintegrating force, selected from the group consisting of carboxymethylamide, cross-linked sodium carboxymethylcellulose, cross-linked polyvinylpyrrolidone, cross-linked hydroxypropylmethyl cellulose, and at least one excipient;
   b) a second "barrier" layer comprising at least one polymeric material selected from the group consisting of hydroxy propylcellulose, methylcellulose and polyvinylalcohols and additionally containing at least one excipient selected from the group consisting of mannitol, talc, polyvinylpyrrolidone and magnesium stearate;
   c) a third layer containing a second portion of the active substance, a disintegrant substance of the type defined in a) and at least one excipient;
   d) a casing comprising a film-forming polymeric materials which is impermeable and insoluble in water having a pH of 7 or less, optionally soluble in alkaline aqueous solutions, selected from the group consisting of ethylcellulose, cellulose acetate propionate, methacry-late polymers, acrylic and methacrylic copolymers and polyvinylalcohols, which casing partially encapsulates the second layer and the third layer.

2. A tablet according to claim 1, wherein said first and third layers each contain from 1% to 95% by weight of said disintegrant substance.

3. A tablet as claimed in claim 1, wherein at least one additional layer containing an active substance is present, and said additional layer is separated from said third layer by a barrier layer comprising at least one polymeric material selected from the group consisting of cellulosic derivatives and polyvinyl alcohols, said barrier layer being gellable or soluble on contact with water or an aqueous liquid.

4. A tablet as claimed in claim 1, wherein the active substance in the first layer is the same as the active substance in the third layer.

5. A tablet as claimed in claim 1, wherein the active substance in the first layer is different from the active substance in the third layers.

6. A tablet as claimed in claim 1, wherein said active substance is present in at least one of said first layer

and said third layer in microencapsulated form.

7. A process for preparing the tablet of claim 1, comprising pressing said first, second, and third layer together to prepare a multilayer tablet, and applying said casing to said multilayer tablet.

8. A process as claimed in claim 7, wherein said casing is applied to said multilayer tablet by at least one method selected from the group consisting of spraying, compression, immersion, and inserting into a preformed casing.

Claims for the following Contracting States: GR and ES

1. Process for the preparation of a pharmaceutical tablet able to release an active substance at successive times, comprising:
   a) a first step carried out by a multilayer tablet press, wherein a first layer is formed which contains portion of the active substance, at least one disintegrant substance which on contact with water or aqueous liquids is able to develop a disintegrating force, selected from the group consisting of carboxymethylamide, cross-linked sodium carboxymethylcellulose, cross-linked polyvinylpyrrolidone, cross-linked hydroxypropylmethyl cellulose, and at least one excipient;
   b) a second step carried out by a multilayer tablet press, wherein a second "barrier" layer next to the first layer is formed, which "barrier" layer comprises at least one polymeric material selected from the group consisting of hydroxy propylcellulose, methylcellulose and polyvinylalcohols and additionally comprises at least one excipient selected from the group consisting of mannitol, talc, polyvinylpyrrolidone and magnesium stearate;
   c) a third step carried out by a multilayer tablet press, wherein a third layer is formed which contains a second portion of the active substance, a disintegrant substance of the type defined in a) and at least one excipient;
   d) a fourth step wherein a casing is formed for housing the second and third layer, said casing being obtained by pressing or spraying or dipping, from a film forming polymeric material which is impermeable and insoluble in water at pH of 7 or less, optionally soluble in alkaline aqueous solutions, selected from the group consisting of ethylcellulose, cellulose acetate propionate, methacrylate polymers, acrylic and methacrylic copolymers and polyvinylalcohols.

2. Process for the preparation of a tablet according to claim 1, wherein said first and third layers each contain from 1% to 95% by weight of said disintegrant substance.

3. Process for the preparation of a tablet as claimed in claim 1, wherein at least one additional layer containing an active substance is formed, and said additional layer is separated from said third layer by a barrier layer comprising at least one polymeric material selected from the group consisting of cellulosing derivatives and polyvinyl alcohols, gellable or soluble on contact with water or an aqueous liquid.

4. Process for the preparation of a tablet as claimed in claim 1, wherein the active substance in the first layer is the same as the active substance in the third layer.

5. Process for the preparation of a tablet as claimed in claim 1, wherein the active substance in the first layer is different from the active substance in the third layers.

6. Process for the preparation of a tablet as claimed in claim 1, wherein said active substance is introduced in at least one of said first layer and said third layer in microencapsulated form.

Revendications

1. Comprimé pour usage pharmaceutique, susceptible de libérer une substance active à des instants successifs, comprenant :
   a) une première couche contenant une première quantité d'une substance active, au moins une substance susceptible de se déliter qui, au contact de l'eau ou de liquides aqueux, est capable de développer une force de désagrégation, choisie parmi le groupe constitué par le carboxyméthylamide, la carboxyméthylcellulose de sodium réticulée, la polyvinylpyrrolidone réticulée, l'hydroxypropyl-

méthylcellulose réticulée et au moins un excipient ;
b) une seconde couche formant "barrière", comprenant au moins une substance polymère choisie dans le groupe constitué par l'hydroxypropylcellulose, la méthylcellulose et des polyvinylalcools et contenant en outre au moins un excipient choisi dans le groupe constitué par le mannitol, le talc, la polyvinylpyrrolidone et le stéarate de magnésium ;
c) une troisième couche contenant une seconde quantité de la substance active, une substance susceptible de se déliter, du type défini en a) et au moins un excipient ;
d) une enveloppe comprenant une substance polymère formant un film, qui est imperméable et insoluble dans l'eau ayant un PH de 7 ou moins, éventuellement soluble dans des solutions alcalines aqueuses, choisie dans le groupe constitué par l'éthylcellulose, le propionate d'acétate de cellulose, des polymères de méthacrylate, des copolymères acryliques et méthacryliques et des alcools polyvinyliques, ladite enveloppe encapsulant partiellement la seconde et la troisième couches.

2. Comprimé selon la revendication 1, dans lequel les première et troisième couches contiennent chacune de 1 % à 95 % en poids de ladite substance susceptible de se déliter.

3. Comprimé tel que revendiqué dans la revendication 1, dans lequel une couche supplémentaire contenant une substance active est présente, et cette couche supplémentaire étant séparée de la troisième couche par une couche formant barrière comprenant au moins une substance polymère choisie dans le groupe constitué par des dérivés cellulosiques et des alcools polyvinyliques, ladite couche de barrière étant gélifiable ou soluble au contact de l'eau ou d'un liquide aqueux.

4. Comprimé tel que revendiqué dans la revendication 1, dans lequel la substance active dans la première couche est la même que la substance active dans la troisième couche.

5. Comprimé tel que revendiqué dans la revendication 1, dans lequel la susbstance active dans la première couche est différente de la substance active dans la troisième couche.

6. Comprimé tel que revendiqué dans la revendication 1 dans lequel la substance active est présente dans au moins l'une des première et troisième couches sous forme micro-encapsulée.

7. Procédé de préparation de comprimés selon la revendication 1, consistant à presser ensemble les première, seconde et troisième couches pour constituer un comprimé multicouches et à appliquer l'enveloppe au comprimé multicouches.

8. Procédé tel que revendiqué dans la revendication 7, dans lequel l'enveloppe est appliquée au comprimé multicouches par au moins un moyen choisi dans le groupe comprenant la pulvérisation, la compression, l'immersion et l'insertion dans une enveloppe préformée.

Revendications pour les Etats contractants suivants: GR et ES

1. Procédé de préparation d'un comprimé pharmaceutique susceptible de libérer une substance active à des instants successifs, comprenant :
a) une première étape effectuée par une presse de comprimés multicouches, dans laquelle on forme une première couche qui contient une fraction de la substance active, au moins une substance susceptible de se déliter qui, au contact de l'eau ou de liquides aqueux est capable de développer une force de désagrégation, choisie parmi le groupe constitué par le carboxyméthylamide, la carboxyméthylcellylose de sodium réticulée, la polyvinylpyrrolidone réticulée, l'hydroxypropylméthylcellulose réticulée et au moins un excipient ;
b) une seconde étape effectuée par une presse de comprimés multicouches, dans laquelle on forme une seconde couche formant "barrière" jouxtant la première couche, ladite couche de barrière comprenant au moins une substance polymère choisie dans le groupe constitué par l'hydroxypropylcellulose, la méthylcellulose et des alcools polyvinyliques et comprenant en outre au moins un excipient choisi dans le groupe constitué par le mannitol, le talc, la polyvinylpyrrolidone et le stéarate de magnésium ;
c) une troisième étape effectuée par une presse de comprimés multicouches, dans laquelle on forme une troisième couche qui contient une seconde fraction de la substance active, une substance susceptible de se déliter, du type défini en a) et au moins un excipient ;

d) une quatrième étape dans laquelle on forme une enveloppe pour recouvrir les seconde et troisième couches, ladite enveloppe étant obtenue par pressage, pulvérisation ou immersion, à partir d'une substance polymère susceptible de former un film qui soit imperméable et insoluble dans l'eau ayant un PH de 7 ou moins, éventuellement soluble dans des solutions alcalines aqueuses, choisie dans le groupe constitué par l'éthylcellulose, le propionate d'acétate de cellulose, des polymères de méthacrylate, des copolymères acryliques et méthacryliques et des alcools polyvinyliques.

2. Procédé de préparation de comprimé selon la revendication 1, dans lequel lesdites première et troisième couches contiennent chacune de 1 % à 95 % en poids de ladite substance susceptible de se déliter.

3. Procédé de préparation de comprimé tel que revendiqué dans la revendication 1, dans lequel on forme au moins une couche supplémentaire contenant une substance active, et cette couche supplémentaire étant séparée de la troisième couche par une couche formant barrière comprenant au moins une substance polymère choisie dans le groupe constitué par des dérivés cellulosiques et des alcools polyvinyliques, gélifiable ou soluble au contact de l'eau ou d'un liquide aqueux.

4. Procédé de préparation de comprimé tel que revendiqué dans la revendication 1, dans lequel la substance active dans la première couche est la même que la substance active dans la troisième couche.

5. Procédé de préparation de comprimé tel que revendiqué dans la revendication 1, dans lequel la substance active de la première couche est différente de la substance active dans la troisième couche.

6. Procédé de préparation de comprimé tel que revendiqué dans revendication 1, dans lequel la substance active est introduite dans au moins l'une des première et troisième couches sous forme micro-encapsulée.

Ansprüche

1. Tablette für pharmazeutische Anwendung, welche imstande ist, eine aktive Substanz in aufeinanderfolgenden Zeiten auszulassen, und welche aus folgenden Komponenten besteht:
   a) eine erste Schicht welche eine erste Portion einer aktiven Substanz, mindestens einer auflösenden Substanz, welche, in Berührung mit Wasser oder mit wässrigen Flüssigkeiten , imstande ist, eine auflösende Kraft zu entwickeln, und welche aus der Gruppe bestehend aus Karboxymethylamid, vernetzten Natriumkarboxymethylzellulose, vernetzten Polyvinylpyrrolidon, vernetzten Hydroxypropylmethylzellulose ausgewählt ist, und wenigstens einen Hilfsstoff enthält;
   b) eine zweite Sperrschicht, welche wenigstens eine polymerischere Substanz aus der Gruppe: Hydroxypropylzellulose, Methylzellulose und Polyvinyalkoholen, und wenigstens einen Hilfsstoff aus der Gruppe: Mannit, Talk, Polyvinylpyrrolidon und Magnesiumstearat enthält;
   c) eine dritte Schicht welche eine zweite Portion der aktiven Substanz, eine auflösende in a) definierte Substanz und wenigstens einen Hilfsstoff enthält;
   d) eine Kapsel, welche ein filmbildendes wasserdichtes und im Wasser von pH 7 oder weniger unlösliches, eventuell in wässrigen alkalischen Lösungen lösliches, polymerisches Material enthält, welches aus der Gruppe bestehend aus Äthylzellulose, Zellulose-Azetat-Propinat, Methakryl-Polymeren, Akryl- und Methalkryl-Mischpolymeren und Polyvinylalkoholen, ausgewählt ist und welche teilweise die zweite und dritte Schicht einkapselt.

2. Tablette gemäss Anspruch 1, in welcher die erste und dritte Schicht je von 1 bis 95 Gew. % der aufflösenden Substanz enthält.

3. Tablette gemäss Anspruch 1, in welcher wenigstens eine weitere Schicht, die eine aktive Substanz enthält, anwesend ist, welche von der besagten dritten Schicht durch eine Sperrschicht getrennt ist, die aus wenigstens einem polymerischen Material besteht, welches aus der Gruppe von zellulosischen Derivaten und Polyvinylalkoholen ausgewählt ist und die besagte Sperrschicht in Berührung mit Wasser oder mit wässrigen Lösungen Gel und löslich wird.

4. Tablette gemäss Anspruch 1, in welcher die aktive Substanz in der ersten Schicht dieselbe als die aktive Substanz in der dritten Schicht ist.

5. Tablette gemäss Anspruch 1, in welcher die aktive Substanz in der ersten Schicht von der aktiven Substanz in der dritten Schicht verschieden ist.

6. Tablette gemäss Anspruch 1, in welcher die besagte aktive Substanz in wenigstens einer der besagten ersten und dritten Schicht in einem mikroeinkapsulierten Zustand anwesend ist.

7. Verfahren zur Herstellung einer Tablette gemäss Anspruch 1, welches das Zusammenpressen der ersten, zweiten und dritten Schicht zur Herstellung einer mehrgeschichteten Tablette und die Auftragung der besagten Kapsel auf der mehrgeschichteten Tablette umfässt.

8. Verfahren gemäss Anspruch 7, in welchem die besagte Kapsel auf der mehrgeschichteten Tablette durch wenigstens eine Methode welche Zerstäubung, Zusammenpressen, Eintauchen und Einsatz in einer vorgeformten Kapsel einschliesst, angebracht wird.

Patentansprüche für folgende Vertragsstaaten :ES, GR

1. Verfahren zur Herstellung einer pharmazeutischen Tablette, welche imstande ist, eine aktive Substanz in aufeinanderfolgenden Zeiten auszulassen, gekennzeichnet durch die folgenden Phasen:
   a) eine erste Phase, in einer Presse für mehrgeschichtete Tabletten durchgeführt, in welcher eine erste Schicht geformt wird, die eine Portion der aktiven Substanz, wenigstens eine auflösende Substanz die, in Berührung mit Wasser oder mit wässrigen Lösungen imstande ist eine auflösende Kraft zu entwickeln und aus der Gruppe bestehend aus Karboxymethylamid, vernetzten Natriumkarboxymethylzellulose, vernetzten Polyvinylpyrrolidon, vernetzten Hydroxypropylmethylzellulose ausgewählt ist, und wenigstens einen Hilfsstoff enthält;
   b) eine zweite Phase, in einer Presse für mehrgeschichtete Tabletten durchgeführt, in welcher eine zweite Sperrschicht neben der ersten Schicht geformt wird, welche Sperrschicht wenigstens eine polymerische Substanz aus der Gruppe bestehend aus Hydroxypropylzellulose, Methylzellulose und Polyvinylalkoholen ausgewählt ist, enthählt und weiter einen Hilfsstoff enthält, welcher aus der Gruppe bestehend aus Mannit, Talk, Polyvinylpyrrolidon und Magnesiumstearat ausgewählt ist;
   c) eine dritte Phase in einer Presse für mehrgeschichtete Tabletten durchgeführt, in welcher eine dritte Schicht geformt wird, die eine zweite Portion der aktiven Substanz, eine auflösende in a) definierte Substanz und wenigstens einen Hilfsstoff enthält;
   d) eine vierte Phase, in welcher eine Kapsel, zur Einschliessung der
   zweiten und dritten Schicht, welche durch Zusammenpressen, Zerstäubung, oder Eintauchen aus einem filmbildenden Polymerisat geformt wird, welches wasserdicht und im Wasser, bei pH 7 oder weniger, und eventuell im wässrigen alkalischen Lösungen, unlöslich ist, und welches aus der Gruppe bestehend aus Äthylzellulose, Zellulose Azetat-Propiconat, Methakrylpolymeren, Akryl- und Methakrylmischpolymeren und Polyvinylalkoholen ausgewählt wird.

2. Verfahren zur Herstellung einer Tablette gemäss Anspruch 1, dadurch gekennzeichnet, dass die erste und die dritte Schicht je von 1 bis 95 Gew. % der besagten auflösenden Substanz enthält.

3. Verfahren zur Herstellung einer Tablette gemäss Anspruch 1, dadurch gekennzeichnet, dass wenigstens eine weitere Schicht, die eine aktive Substanz enthält, geformt wird, welche durch eine Sperrschicht von der besagten dritten Schicht getrennt ist, welche Sperrschicht wenigstens ein Polymerisat aus der Gruppe bestehend aus Zellulosderivaten und Polyvinylalkoholen enthält, und in Berührung mit Wasser oder einer wässrigen Lösung Gel oder löslich wird.

4. Verfahren zur Herstellung einer Tablette gemäss Anspruch 1, dadurch gekennzeichnet, dass die aktive Substanz in der ersten Schicht dieselbe als die aktive Substanz in der dritten Schicht ist.

5. Verfahren zur Herstellung einer Tablette gemäss Anspruch 1, dadurch gekennzeichnet, dass die aktive Substanz in der ersten Schicht von der aktiven Substanz in der dritten Schicht verschieden ist.

6. Verfahren zur Herstellung einer Tablette gemäss Anspruch 1, dadurch gekennzeichnet, dass die aktive

Substanz in wenigstens einer der besagten ersten und dritten Schicht in Mikrokapselform eingeführt wird.

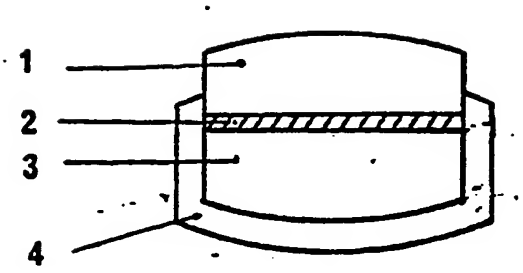

FIG. 1